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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/359,672	BLACKBURN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,35-40,42,43,47,49,50 and 55-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,35-40,42,43,47,49,50 and 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed on 8/15/2003 has been entered.

Amended claims 33, 35-40, 42-43, 47, 49-50 and 55-58 are pending in the present application, and they are examined on the merits herein.

New Matter

Amended claims 37-40, 42-43, 47 and 49-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new ground of rejection necessitated by Applicants' amendment.**

Claim 37 and its dependent claims recite "(ii) if the cell is the differentiated progeny of a cell selected from the group consisting of an ES cell, an EC cell, and an EG cell, determining whether said differentiated progeny differentiates further". There is literally no support in the originally filed specification for an *in vitro* method of assaying whether a DNA under investigation codes for a polypeptide that directs transport of a cell active to a cell surface by determining whether a differentiated progeny of a mouse ES, EC or EG cell further differentiates as claimed. Applicants fail to point out the specific page number and line number in the present specification that provide support for such a method. While the specification teaches in general that due to their pluripotent and proliferative character, key cellular processes such as viability,

propagation, and differentiation can be analyzed in transfected ES cells (page 12, first paragraph and example 4) , there is no teachings or literal support for the step of determining whether the differentiated progeny of a mouse ES, EC or EG cell differentiates further in the in vitro assay method as claimed. Therefore, given the lack of written support on this aforementioned issue from the originally filed specification, it would appear that Applicants did not have possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 37-40, 42-43, 47 and 49-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth immediately above. **This is a new ground of rejection necessitated by Applicants' amendment.**

As enablement requires the specification to teach how to make and use the claimed invention, with the lack of sufficient description and/or guidance provided by the instant specification at the time the application was filed regarding to an *in vitro* method of assaying whether a DNA under investigation codes for a polypeptide that directs

transport of a cell active to a cell surface by determining whether a differentiated progeny of a mouse ES, EC or EG cell further differentiates as claimed, it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Amended claims 35 and 56-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new ground of rejection necessitated by Applicants' amendment.**

In claim 35, it is unclear what is encompassed by the phrase "the mouse cell of step (c)". Which particular mouse cell among **the mouse cells** of step (c)? The metes and bounds of the claim are not clearly determined. Additionally, on line 3 of the claim there is a long space between the terms "of" and "cDNA", it is unclear whether the claim is complete or not as written. Clarification is requested because the metes and bounds of the claim are not clearly determined.

Claim 56 recites the limitation "said second vector contains a DNA that codes for an anti-sense RNA" in lines 1-2 of the claim. There is insufficient antecedent basis for this limitation in the claim. In claim 33 which claim 56 is dependent on, the second

vector only contains a DNA coding for a selectable marker and a cDNA coding for the protein or polypeptide or other product of cDNA expression.

In claim 57, the limitation "further comprising the step: (e) isolating said cDNA coding for the protein or polypeptide or other product of cDNA expression" renders the claim indefinite. This is because in claim 33 which claim 57 is dependent on, step (e) is assaying the biological effect of expression of the protein or polypeptide or other product of cDNA expression. It is unclear what exactly Applicants intend to claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 33, 35-36, 55-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gassmann et al. (Proc. Natl. Acad. Sci. 92:1292-1296, 1995, IDS) in view of Carstens et al. (Gene 164:195-202, 1995, Cited previously) and Cooper et al. (U.S. Patent No. 5,770,374 with an effective filing date at least to 11/12/1993). **This is the same ground of rejection already set forth in the previous Office Action mailed on 2/12/03 (pages 11-15).**

Gassmann et al. disclose as an exemplification the preparation of mouse ES clone 1.19 cells that contain episomal pMGD20neo DNA and express the polyoma large T antigen. These clonal cells further support the replication, episomal maintenance and expression of hygromycin B under the control of the phosphoglycerate kinase promoter of a second plasmid PGKhphΔLT20. The second plasmid also contains the polyoma *ori*, and a large T gene with a 1249-bp deletion in the coding sequence (page 1295, column 1, see entire first paragraph). For further details on the disclosed pMGD20neo and PGKhphΔLT20 vector plasmids, please refer to Fig. 1. Gassmann et al. teach that the yield of hygromycin B-resistant clones was about 100 times greater with PGKhphΔLT20 than with the control plasmid PGKhph that lacks the polyoma segment (page 1295, col. 1, first full paragraph). This has been attributed to the ability of the PGKhphΔLT20 DNA to replicate from its own ori in the presence of large T provided by the already established episomal pMGD20neo DNA. Gassmann et al. specifically teach that plasmid(s) containing a polyoma ori, a selectable marker and any other gene(s) of interest could be established and maintained in transfected cells with preexisted or established presence of polyoma large T, e.g., mouse ES clone 1.19 cells that contain

episomal pMGD20neo plasmid, and that the capability to establish plasmids as episomes in ES cells should find utility for a variety of studies of gene regulation in these cells; e.g., gene expression, molecular complementation, DNA replication and recombination and genetic control of differentiation in ES cells and during murine embryogenesis (page 1296, col. 1, bottom of the second full paragraph and top paragraph of col. 2).

Gassmann et al. do not specifically teach the *in vitro* assay of claim 33, wherein the second vector contains a cDNA coding for a protein, a polypeptide or other product of cDNA expression (e.g., an antisense RNA) or wherein further comprising the step of isolating the DNA coding for the protein or polypeptide or other product of cDNA expression. Nor do Gassmann et al. teach explicitly a method of screening a library of cDNAs using the method of claim 33.

However, at the effective filing date of the present application, Carstens et al. already disclose an EBV-based episomal vector system that allows functional cloning of regulatory genes by expression of libraries of cDNA inserts either in the sense or antisense direction (see abstract). Carstens et al. further teach that generally, although it is sufficient to place EboriP and the EBNA-1 (viral replication factor) gene on the same vector and vectors harboring both elements have been successfully used to clone genes from expression libraries in human cells, vector/host systems expressing EBNA-1 **in trans** have been reported to be **more efficient** in generating stable, transfected colonies of human cells than systems in which EBNA-1 is only provided by the vector

(page 196, col. 2, under the section "Construction and properties of CMV-EL and C1E-EL").

Cooper et al. also teach that Epstein-Barr virus (EBV)-based episomes have been used to efficiently screen cDNA libraries (col. 1, lines 58-62). Cooper et al. also teach an episomal vector system for expressing a foreign gene in a mammalian cell as well as for cDNA library cloning (see Summary of the Invention). Specifically, Cooper et al. teach that their episomal vector system can be used to identify potentially novel dominant oncogenes and/or antioncogenes that are involved in tumor progression by both sense and anti-sense cDNA library screening (col. 17, lines 9-33).

Accordingly, it would have been obvious and within the level of skill for an ordinary artisan to adapt the episomal plasmid vector system taught by Gassmann et al. for screening both sense and antisense cDNA libraries for genes involved in the differentiation of mouse ES cells and/or during murine embryogenesis in light of the teachings of Carstens et al. Cooper et al. It would also have been obvious for an ordinary skilled artisan to divide mouse ES cells harbouring a first episomal vector expressing polyoma large T antigen into two distinct cell populations for subsequent transfections with two distinct episomal vectors coding for different gene products to assay for their biological effects.

One of ordinary skilled in the art would have been motivated to carry out the above modification because the episomal vector system taught by Gassmann et al. provides the viral replication factor *in trans*, which has been reported to be efficient in generating stable transfected cells as well as it allows the utilization of rodent cells in

the screening of cDNA libraries because of the inherent limitation of the EBV-based shuttle vector system (applicable for most mammalian cells with the exception of rodent cells; see Carstens et al., page 196, col. 2, top of the second paragraph). Moreover, one of ordinary skilled artisan would have a reasonable expectation of success because Gassmann et al. have demonstrated successfully by exemplification that mouse ES cells containing episomal pMGD20neo DNA and expressing the polyoma large T antigen (supplied in *trans*) support an efficient replication, episomal maintenance and expression of hygromycin B of a second plasmid PGKhphΔLT20 containing the polyoma *ori*.

Therefore, the claimed invention was *prima facie* obvious in the absence of evidence to the contrary.

Response to Applicants' argument

Applicants' arguments related to the above rejection in the Amendment filed on 8/15/2003 (pages 14-15) have been fully considered, but they are not found persuasive.

Applicants argue mainly that Gassmann does not describe expression of a cDNA from the second vector, or how to go about achieving this, and Gassmann does not teach how to screen cDNA libraries using his two vectors system. Applicants further argue that a skilled person could not have read Gassmann in conjunction with Carstens and Cooper since they represent conflicting document spread over different and divergent fields of art. For example, Carstens is performed in non-ES cells and utilizes a replication factor system based on Epstein-Barr virus that can not be performed in

rodent cells, and that Carstens et al. teach the use of one vector system in human fibroblasts utilizing a replication factor system that could not be used in mouse cells as currently claimed in the present invention. Cooper describes a one-vector system in human bladder carcinoma cells and does not add anything further. As such, Gassmann, Carstens and Cooper could not be reasonably combined in order to render the present amended claims obvious.

Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

In response to applicant's argument that the teachings of Gassmann, Carstens and Cooper represent conflicting documents spread over different and divergent fields of art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Gassmann clearly discloses a system to establish **plasmids as episomes in mouse ES cells**. Gassmann teaches specifically that plasmid(s) containing a polyoma ori, a selectable marker and any other gene(s) of interest could be established and maintained in mouse ES cells expressing large T antigen provided by an already established episomal vector. Gassmann further teaches that the episomal vector system has utility for a variety of studies of gene regulation in mouse ES cells; e.g., gene expression, molecular complementation, DNA replication and recombination and genetic control of differentiation in ES cells and during murine embryogenesis

(page 1296, col. 1, bottom of the second full paragraph and top paragraph of col. 2). Carstens discloses an EBV-based episomal vector system that allows functional cloning of regulatory genes by expression using a library of cDNA inserts in both sense and anti-sense orientations using EBNA-1 producing MSU1.1 clones which have been previously transfected with an EBNA-1 expression vector. Cooper also teaches that EBV-based episomes have been used efficiently to screen cDNA libraries and disloses episomal plasmids containing a papovirus origin of replication and an encoded papovavirus large T antigen mutant form for expression of a heterologous gene in mammalian cells as well as for cDNA library cloning. Therefore, it would have been obvious for an ordinary artisan to adapt the episomal plasmid vector system taught by Gassmann to screen cDNA libraries for genes involved in the differentiation of mouse ES cells and/or during murine embryogenesis. One of ordinary skilled in the art would have been motivated to carry out the above modification because the episomal vector system taught by Gassmann et al. provides the viral replication factor *in trans*, which has been reported to be efficient in generating stable transfected cells as well as it allows the utilization of rodent cells in the screening of cDNA libraries because of the inherent limitation of the EBV-based shuttle vector system (applicable for most mammalian cells with the exception of rodent cells; see Carstens et al., page 196, col. 2, top of the second paragraph). Furthermore, Examiner notes that Applicants attempted to claim an *in vitro* assay method utilizing a mouse ES, EC, EG or a differentiated progeny thereof using an episomal vector system that is dependent on the provision of EBNA-1 antigen (see previous claim 55), until the enablement issue was

raised by the Examiner. Thus, it is clear that the teachings of Gassmann, Carstens and Cooper do not represent conflicting documents spread over different and divergent fields of art as asserted by Applicants.

Accordingly, amended claims 33, 35-36 and 55-58 are rejected under 35 U.S.C. 103(a) for the reasons set forth above.

Amended claims 37-40, 42-43 and 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gassmann et al. (Proc. Natl. Acad. Sci. 92:1292-1296, 1995, IDS) in view of Carstens et al. (Gene 164:195-202, 1995, Cited previously) and Cooper et al. (U.S. Patent No. 5,770,374 with an effective filing date at least to 11/12/1993) as applied to claims 33, 35-36 and 55-58 above, and further in view of Lok (U.S. Patent No. 5,753,462), Williams et al. (Nature 336:684-687, 1988; Cited previously), Moreau et al. (Nature 336:690-692, 1988; Cited previously) and Nichols et al. (Exp. Cell Res. 215:237-239, 1994).

The combined teachings of Gassmann et al., Carstens et al. and Cooper et al. have been discussed and applied as above. However, none of the references specifically teaches an *in vitro* method for assaying or screening for a DNA codes for a polypeptide that directs transport of a cell active protein to a cell surface, wherein the cell active protein inhibits differentiation of the cell and in the absence of the cell active protein the cell will differentiate.

At the effective filing date of the present application, Lok already teaches a method for trapping signal sequences as a strategy for cloning cDNA of unidentified

secreted and transmembrane proteins, particularly those involved in signal transduction (see abstract). Lok teaches that the expression vectors comprising the following operably linked elements: a transcription promoter; a first DNA segment encoding a cloning site for insertion of a 5' terminal DNA fragment; a second DNA segment encoding a leader-less protein, whereby in-frame joining of the second DNA segment with the first DNA segment provides cell surface expression of the leader-less protein if a functional signal sequence is inserted in the cloning site; and a transcription terminator (col. 2, lines 11-19). Lok further teaches the various approaches available for detection/selection of signal sequence cDNAs, including a biological selection procedure exemplified by a prototype in which the leader-less protein encoded by the expression vector is a cytokine receptor (including IL-6 receptor) or a growth factor receptor, and when such receptor is introduced into a factor-dependent cell line, cell surface expression of the receptor permits cell proliferation (i) in the presence of the receptor's corresponding cytokine or growth factor, and (ii) in the absence of the factor(s) upon which the starting cell-line is dependent (see cols. 8-9). Additionally, Lok teaches that such biological selection protocol is an attractive alternative to automated cell sorting/selection since it does not require an expensive specialized piece of equipment and can be conveniently performed in most laboratory settings (col. 11, lines 28-33).

Also at the effective filing date of the present application, Williams et al. already teach that in the presence of a secreted leukemia inhibitory factor (LIF), mouse ES cells retain the stem cell phenotype of compact colonies of small cells with a large nuclear to

cytoplasmic ratio *in vitro*, whereas ES cells maintained in normal culture medium without LIF differentiate into colonies containing large, flat differentiated cells over a period of 3-6 days (page 684, column 2, last paragraph continues to top of column 1, page 685). Moreau et al. already disclose the complete cDNA sequence for a secreted LIF (Fig. 1). Nichols et al. also teach that mouse ES cells do not express IL-6 specific receptor component, and are therefore unresponsive to IL-6 alone. However, in the presence of a complex of IL-6/sIL-6R mouse ES cell lines can be maintained *in vitro* in an undifferentiated state similar to those in the presence of LIF (see page 237 in the Introduction). This result also suggests that mouse ES cells expressing exogenous functional IL-6 receptors in the presence of IL-6 can retain the stem cell phenotype *in vitro*.

Accordingly, it would have been obvious and within the skill level of an ordinary artisan to modify the episomal vector system taught by Gassmann et al. for cloning or screening DNAs coding for unidentified secreted proteins and membrane proteins based on the signal sequence trap approach by expressing a composite DNA in a polyoma virus-based shuttle vector system in mouse ES cells, in which a DNA coding for a leaderless leukemia inhibitory factor (LIF or IL-6) or a leaderless IL-6 receptor is used to trap NH2-terminal signal encoded sequences, and select for cells containing DNA coding for signal sequences under suitable conditions based on the differentiation state of mouse ES cells in culture, in light of the combined teachings of Carstens et al., Cooper et al., Lok, Williams et al., Moreau et al. and Nichols et al.

It would have been obvious for an ordinary skilled artisan to select biological conditions known in the art regarding to the differentiation state of ES cells in culture to select for mouse ES cells containing DNA coding for signal sequences because of the distinct phenotypes exhibited between differentiated or non-differentiated ES cells in culture, and that when an ordinary skilled artisan utilizes ES cells in any studies, the differentiation state of the utilized ES cells is always an issue that is addressed. For example, in disclosing the maintenance of an extrachromosomal plasmid vector system in mouse embryonic stem cells, Gassmann et al. concern about whether the expression of polyoma large T would affect the ES cell's totipotency, but also suggest studies for investigating molecular mechanisms in differentiating ES cells (see last paragraph on col. 1 of page 1296 continues to col. 2).

One of ordinary skill in the art would have been motivated to carry out the above modification because the polyoma virus-based shuttle vector system in mouse ES cells taught by Gassmann et al. offers various advantages as already noted by Carstens et al. for a similar Epstein-Barr virus based shuttle vector system. These advantages include a) easy recovery of the library vectors from selected clones, (b) expression level of the cDNA expression cassette is unaffected by integration, and (c) no cDNA expression cassettes are lost due to disruption of the vector following integration into genomic DNA (see Carstens et al., page 196, column 1, last paragraph continues to the top of column 2). Moreover, unlike the Epstein-Barr virus based shuttle vector system, the polyoma virus-based shuttle vector system of Gassmann et al. is applicable to both mammalian cells and rodent cells (e.g., mouse ES cells) as well as its capability to

provide the viral replication factor *in trans*, which has been reported to be efficient in generating stable transfected cells. Furthermore, one of ordinary skilled artisan would have been motivated to carry out the above modification because it would allow an easy biological selection procedure for identification of a mouse ES cell containing a DNA sequence coding for a signal polypeptide on the basis of its induced morphological or proliferative change due to the presence or absence of a secreted LIF or in the presence of absence of a functional IL-6 receptor.

Thus, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Response to Applicants' argument

Applicants' arguments related to the above rejection in the Amendment filed on 8/15/2003 (page 16) have been fully considered, but they are not found persuasive.

Once again, Applicants argue the lack of compatibility between Gassmann, Carstens and Cooper as presented in the response to the rejection of claims 33, 35-36 and 55-58 above. Applicants further argue that it is not reasonable to assume a skilled person could have taken and applied techniques describe for use in human somatic cell lines and expected these to function in an identical and analogous matter in mouse embryonic stem cells, embryonic carcinoma cells or embryonic gonadal cells. Applicants further argue that at the very least, a skilled artisan would be forced to undertake undue levels of experimentation in order to generate a system that was functional in ES cells.

Applicants' arguments are not found persuasive for the following reasons.

(1) With respect to the lack of compatibility between Gassmann, Carstens and Cooper, Applicants' arguments are not found persuasive for the reasons already stated in the response to Applicants' arguments on the rejection of claims 33, 35-36 and 55-58 above.

(2) With respect to the issue of undue burden or experimentation for a skilled artisan to generate a system that is functional in ES cells, and there is not a reasonable expectation of success, Gassmann already demonstrated the feasibility of a system to establish **plasmids as episomes in mouse ES cells**, and teach specifically that plasmid(s) containing a polyoma ori, a selectable marker and any other gene(s) of interest could be established and maintained in mouse ES cells expressing large T antigen provided by an already established episomal vector. Moreover, apart from the exemplification showing the expression of various cDNAs solely in mouse ES cells, Applicants did not show any cDNA expression in mouse EG, EC cells or any differentiated progeny thereof using the episomal vector system of the present invention or actually used the described vector system to screen for genes that code for secreted and cell surface proteins (example 4 is prophetic). Is it also undue burden experimentation for the Applicants to carry out the presently claimed invention?

In light of the teachings of Gassmann, Carstens, Cooper, Lok and others, coupled with a high level of skills of an ordinary skilled artisan in the art at the effective filing date of the present application, one has a reasonable expectation of success to carry out the presently claimed invention.

Accordingly, amended claims 37-40, 42-43 and 47-50 are rejected under 35 U.S.C. 103(a) for the reasons stated above.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D. Gerald D. Leffers Jr.
GERRY LEFFERS
PRIMARY EXAMINER